Docket No.: 01-22 US

REMARKS

STATUS SUMMARY

Claims 1 – 45 are pending in the present application. Claims 41 – 45 have been withdrawn without prejudice as being drawn to non-elected subject matter, and accordingly have been canceled herein. Claims 1 – 40 presently stand rejected. Claims 1, 6 – 8, 16, 20, 35 and 36 have been amended herein. Claims 41 – 45 have been canceled herein.

RESTRICTION REQUIREMENT

As indicated in the above-referenced Office Action, a provisional election was made without traverse on October 16, 2003 to prosecute the subject matter of Group I, claims 1 – 40. Applicants hereby affirm the election of claims 1 – 40. Accordingly, claims 41 – 45 have been canceled herein without prejudice.

CLAIM REJECTIONS – 35 U.S.C. § 112

Claims 6, 8 and 20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

As to claim 6, the Examiner contends that it is not clear what the expression "optically aligned with the light-reflective surface" means. Applicants submit that one of ordinary skill in the art would construe the quoted expression as meaning that the fiber optic end is positioned relative to the light reflective surface such that an optical signal can be transmitted from the fiber optic end to the light-reflective surface, or from the light-reflective surface to the fiber optic end.

Applicants thus believe that claim 6 is definite under 35 U.S.C. § 112, second paragraph. However, for purposes of clarifying this expression and expediting the allowance of claim 6, Applicants have amended claim 6 to recite "the first fiber-optic end aligned with the light-reflective surface for optical transmission thereto", and "the second fiber-optic end aligned with the light-reflective surface for optical transmission therefrom".

Also as to claim 6, the Examiner contends that it is unclear what type of "light-reflective surface" is considered, since the specification does not support such terminology. Applicants submit that the specification and claim 6, as originally filed, do in fact support this terminology. The specification discusses, as one embodiment, the use of a mirror to reflect light. While the terms "mirror" and "light-reflective surface" may not be coextensive in terms of design or materials used, both terms connote a component capable of reflecting light. One of ordinary skill in the art could readily understand the type of element needed to provide a "mirror" or "light-reflective surface" in the embodiments described in the specification. *See, e.g.,* specification at page 20, line 26 to page 21, line 4. In order to improve consistency as between the specification and claim 6, Applicants have amended the specification at page 20, line 8, to recite "<u>a suitable light-reflective surface such as</u> a mirror **127**." Support for this amendment is found, e.g., in claim 6 as originally filed, and in Figures 3 and 4C.

As to claim 8, the Examiner contends that the expression "each optical fiber output line communicating . . . in opposing, optically-aligned relation to the optical fiber input line" is unclear and not supported by the specification. Applicants submit that this expression is indeed supported by the specification at, for example, page 21, lines 30-31, and Figure 5C. However,

Applicants have amended claim 8 by deleting the term "optically-aligned" as not being needed to define the subject matter claimed.

As to claim 20, the Examiner contends that it is not apparent what the expression "each first fiber-optic end is disposed in spaced, optical alignment with its corresponding second fiber-optic end" means. Applicants submit that this expression is indeed supported by the specification at, for example, page 21, lines 30-31, and Figure 5C. However, Applicants have amended claim 20 by deleting the quoted expression as not being needed to define the subject matter claimed, and by adding "for providing an optical path through the flow cell" for clarification. Claim 36 has also been similarly amended.

In view of the foregoing, Applicants respectfully submit that claims 6, 8 and 20 as amended are definite under 35 U.S.C. § 112, second paragraph, and therefore request that the rejection to these claims be withdrawn at this time.

CLAIM REJECTIONS – 35 U.S.C. § 102

Claims 1 – 3, 5 and 6 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent 6,580,507 to Fry et al. (hereinafter "Fry et al."). Applicants respectfully traverse this rejection because Fry et al. fail to teach each and every element or feature of the rejected claims as amended.

Claim 1 has been amended herein to clarify the structure of the "probe" as a component in which the optical lines are disposed, as follows: "a plurality of probes, each probe comprising a tip at least partially disposed within the manifold body, an optical fiber input line disposed within

the tip, and an optical fiber output line disposed within the tip, each optical fiber input line and optical fiber output line communicating with a corresponding one of the flow cells."

Fry et al. fail to teach a probe as recited in claim 1. Each embodiment disclosed in Fry et al. is a body in which a parallel set of longitudinal bores are formed for transmitting light along an axial direction from a light source to a detector. While Figure 1c of Fry et al. shows optical fibers communicating with one end of the flow cells, Fry et al. fail to teach any form of an optical line-containing probe having any portion "at least partially disposed within the manifold body".

Claim 2 recites that "the manifold body has a plurality of apertures and each probe extends out of a corresponding one of the probe apertures." Fry et al. fail to teach a probe as recited in claim 2.

Claim 3 recites that "the probes are removable from the manifold body." Fry et al. fail to teach a probe as recited in claim 3.

Claim 5 recites that "each probe at least partially defines a corresponding one of the flow cells." Fry et al. teach only that flow cells are completely defined by a monolithic body, and not by any form of a probe.

Claim 6 has been amended herein for the sole purpose of addressing the rejection under 35 U.S.C. § 112. Claim 6 recites that "each probe includes a light-reflective surface facing an interior of the flow cell." Fry et al. fail to teach a light-reflective surface. Claim 6 also recites that "each optical fiber input line terminates at a first fiber-optic end in the probe", and "each optical fiber output line terminates at a second fiber-optic end in the probe". Fry et al. fail to teach a probe in which fiber optic ends reside.

In view of the foregoing, Applicants respectfully submit that claim 1 as amended, and claims 2 – 3, 5 and 6, are patentable under 35 U.S.C. § 102(e) over Fry et al., and therefore request that the rejections to these claims be withdrawn at this time.

CLAIM REJECTIONS – 35 U.S.C. § 103

Claims 1 – 40 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,060,024 to Hutchins et al. (hereinafter "Hutchins et al.") in view of U.S. Patent No. 6,174,497 to Roinestad et al. (hereinafter "Roinestad et al."). The Examiner contends that Hutchins et al. disclose a dissolution testing system and six cells placed in a unitary manifold. The Examiner concedes that Hutchins et al. do not disclose a plurality of probes comprising optical fiber input and output lines going through the flow cells with the light path formed by the inlet and outlet optical fiber lines transverse to the flow through the flow cells. However, the Examiner contends that it would have been obvious "to slightly modify Hutchins by substituting six cells in UV analyzer with the flow cells provided with the fiber optical probes, as disclosed by Roinested, because it gives more flexibility in varying test parameters, such as the number of flow cells required for simultaneous measurements of multiple solutions, which is not restricted by the number of cells provided by UV spectrometer."

As to each rejected claim, Applicants respectfully traverse this rejection because no suggestion or motivation has been shown for modifying or combining Hutchins et al. and Roinestad et al. as proposed by the Examiner, with any reasonable expectation of success, and Hutchins et al. and Roinestad et al. in combination fail to teach or suggest the subject matter recited.

Claims 1 – 7:

In the present application, claim 1 is directed to a "manifold device for use in sample measurements". Claim 1 recites that the manifold device comprises "a plurality of liquid input lines", "a plurality of liquid output lines", and "a plurality of probes". Hutchins et al. and Roinestad et al. fail to teach, suggest or provide motivation for any form of a manifold device for use in sample measurements.

As noted by the Examiner, Figure 6 of Hutchins et al. shows a "six cell UV analyzer" (115) as part of a dissolution testing system. This analyzer is a conventional UV spectrophotometer equipped with more than one sample cell. Hutchins et al. fail to disclose or suggest any particular structure or design for a manifold device as recited in claim 1. Moreover, as conceded by the Examiner, Hutchins et al. fail to disclose or suggest probes.

Roinestad et al. fail to cure the deficiencies of Hutchins et al. Roinestad et al. fail to disclose or suggest any form of a manifold device in which optical probe-type components are integrated. The section of the disclosure by Roinestad et al. cited by the Examiner, col. 7, lines 24-33, relates to the use of conventional dip probes. *See, e.g.,* Roinestad et al. at col. 7, lines 16 & 19. As shown in Figure 3 of Applicants' specification and the description pertaining thereto, conventional dip probes do not include liquid input and output lines. A conventional dip probe is designed to be inserted directly into a test vessel. Media enters an opening at the tip of the dip probe for exposure to light conducted through the dip probe. Accordingly, because they are conventionally intended only for *in situ* testing (i.e., direct insertion in test vessels), such dip probes neither include nor require any means for routing liquid to and from their openings.

Moreover, the approach taken by Applicants in acquiring optical data—i.e., using a manifold device—is quite different from conventional use of separate, *in situ* dip probes and avoids or ameliorates certain disadvantages known to be associated with dip probes, as explained throughout Applicants' specification. *See, e.g.*, Applicants' specification at p. 6, line 31 to p. 7, line 8; p. 9, lines 16-17 ("In operation, such flow cells [as disclosed in Applicants' specification] would not be inserted into the vessels in which dissolution is effected"); p. 9, lines 28-32; and p. 10, lines 4-7.

Moreover, the combined disclosures of Hutchins et al. and Roinestad et al. fail to provide motivation for a manifold device as recited in claim 1. Applicants' specification discusses the advantages of providing a manifold device comprising probes, such as the ability to situate flow cells remotely from analyzing equipment such as a spectrophotometer by providing liquid input and output lines, and enabling the recovery of not only liquid media but also the sample measured so as to preserve the volume of the matrix in a dissolution test vessel. *See, e.g.*, Applicants' specification at p. 15, lines 22-25 ("This latter feature enables the respective lengths of the various liquid lines associated with flow cells $\mathbf{F_1}$ - $\mathbf{F_6}$ to be significantly reduced, which in turn reduces any signal noise or other deleterious effects caused by the circulation of samples in and out of test vessels $\mathbf{V_1}$ - $\mathbf{V_6}$"); and p. 17, lines 6-8 ("by recycling media back into vessels $\mathbf{V_1}$ – $\mathbf{V_6}$, the respective media volumes of test vessels $\mathbf{V_1}$ – $\mathbf{V_6}$ are not reduced as a consequence of the test runs"). Neither Hutchins et al. nor Roinestad et al. suggests that a manifold structure comprising optical probes could provide these or any other advantages, and no motivation has been shown to exist for integrating separate probes into a manifold so as to define flow cells through which both liquid and optical paths can be established.

Furthermore, Applicants' specification specifically distinguishes the disclosures of both Hutchins et al. and Roinestad et al. as being approaches over which Applicants' disclosure offers improvements and/or alternatives. *See, e.g.*, Applicants' specification at p. 4, lines 14-19; and p. 6, line 14 to p. 7, line 8. As shown in Figure 6 of Hutchins et al. and the written description pertaining thereto, volumes of sample media are aspirated from test vessels (31) and pumped through sampling lines (17) into the 6-cell UV analyzer (115). Hutchins et al. fail to disclose any ability to recover these volumes, whether through the use of a manifold with liquid input and output lines or otherwise. Instead, the sample media are diverted to waste. Hutchins et al., col. 4, lines 48-49 ("Any excess media sample is discharged through a line 132 into the waste manifold 97"). While Hutchins et al. employ a "media replacement unit 141" (*see* Hutchins et al., col. 5, lines 4-15), this unit serves only to replace or replenish the volume of liquid in the test vessels, rather than recover or recycle the sample-media matrix that has been sent to a flow cell. Therefore, because Hutchins et al. did not contemplate routing sample media back to the test vessels from the 6-cell UV analyzer, there would not have been any need for providing a manifold device having both liquid input and output lines.

Roinestad et al., as shown in their Figure 11, teach a system in which a fiber optic dip probe is inserted in each test vessel, and each probe optically communicates with its own dedicated detector. As well known by persons skilled in the art, the approach taken by Roinestad et al.—that of *in situ* dissolution testing—is specifically intended to avoid the removal of sample media from test vessels, and therefore Roinestad et al. teach away from the use of a manifold device having liquid input and output lines. Unlike the system disclosed by Hutchins et al., a system for effecting *in situ* dissolution testing such as disclosed by Roinestad et al. contains no

fluid circuitry means at all. It is well known that advocates of *in situ* dissolution testing of the type disclosed in Roinestad et al. consider the elimination of fluid circuitry means to be an advantage over systems that do involve removal of media from test vessels. Therefore, it would not be reasonable to consult the teaching of Roinestad et al. to modify the analyzer of Hutchins et al. so as to obtain the manifold device recited in claim 1. Moreover, Roinestad et al. provide a different solution to the problems of hydrodynamic effects created by dip probes residing in test vessels and the loss of dissolution media. Instead of avoiding the use of dip probes directly in test vessels and removing sample media from the test vessel as disclosed in the present application, Roinestad et al. integrate their dip probes into the agitation shafts operating in the test vessels. *See* Roinestad et al. at Figs. 12 & 13; and col. 14, lines 34-40 & 63-67. Therefore, Roinestad et al. fail to provide any motivation for adopting an approach that enables *ex situ* data acquisition as opposed to *in situ* data acquisition.

Claims 2 – 7 depend or ultimately depend from claim 1, and recite features not taught, suggested or motivated by the combined disclosures of Hutchins et al. and Roinestad et al., at least for the same reasons as regards claim 1.

Claims 8 – 11:

Independent claim 8 is directed to a "manifold device for use in sample measurements". Claim 8 recites that the manifold device comprises "a plurality of flow cells", "a plurality of liquid input lines", "a plurality of liquid output lines", "a plurality of optical fiber input lines", and "a plurality of optical fiber output lines". Hutchins et al. and Roinestad et al. fail to teach,

suggest or provide motivation for any form of a manifold device for use in sample measurements, as discussed hereinabove with regard to claim 1.

Claims 9 – 11 depend from claim 8, and recite features not taught, suggested or motivated by the combined disclosures of Hutchins et al. and Roinestad et al., at least for the same reasons as regards claim 8.

Claims 12 – 32:

Independent claim 12 is directed to a "dissolution media sampling system." Claim 12 recites "a plurality of test vessels" and "a plurality of remote flow cells". The combined disclosures of Hutchins et al. and Roinestad et al. fail to teach, suggest, or provide motivation for a dissolution media sampling system as recited in claim 12, at least for reasons discussed hereinabove with regard to claim 1.

Claims 13 – 32 depend or ultimately depend from claim 8, and recite features not taught, suggested or motivated by the combined disclosures of Hutchins et al. and Roinestad et al., at least for the same reasons as regards claim 12.

Additionally, with respect to claims 22 – 29, it will be noted that Roinestad et al. clearly teach away from the approaches taken by Applicants for calibration. As noted by the Examiner, Roinestad et al. teach the use of software to perform calibration. In the present application, Applicants specifically distinguished such an approach as follows:

> In conventional fiber-optic techniques, a fiber-optic probe is placed directly into the dissolution media and hence its method is described as "in-situ". Unfortunately, particulates in the media tend to interfere with the UV scan and consequently produce inaccurate data. Appropriate software programs can be used to compensate for the inconsistencies caused by the particulates. However,

> because each drug sample (e.g., tablet) has unique particulate features, every sample being tested requires a separate algorithm for correcting the errors caused by the particulates of the tablet. Moreover, fiber-optic probes induce turbulence in the dissolution media. Current fiber-optic techniques are also disadvantageous in that they require calibration prior to each test run. First, "standard" media must be put into a test tube and placed over the fiber-optic probe. Second, "blank" media" must be put into a test tube and placed over the fiber-optic probe. The test is then initiated and the UV data is acquired.

Applicants' specification, p. 6, lines 3-13.

The present application also discusses advantages over prior calibration approaches such as that taught by Roinestad et al. as follows:

> As a result, software-effected adjustments are not required, and all dosages can be tested without software modifications. The invention further provides an arrangement of liquid flow circuitry that enables calibration of all flow cells to be effected simultaneously and in an automated manner.
>
> . . . The system uses the appropriate media at the time the system is being calibrated, thereby eliminating any user intervention and also significantly reducing calibration time. All eight vessels can be calibrated at the same time with this system, unlike the existing method that requires each vessel to be manually calibrated one vessel at a time with the use of a test tube.

Applicants' specification, p. 10, lines 6-9 & 18 – 22.

Claims 33 – 38:

Independent claim 33 is directed to a "dissolution media preparation and/or testing apparatus." Claim 33 recites "a plurality of flow cells supported by the frame and disposed in remote relation to the vessel-holding apertures. Claim 33 further recites "a plurality of liquid input lines", "a plurality of liquid output lines", "a plurality of optical fiber input lines", and "a plurality of optical fiber output lines", each of which is "communicating with a corresponding one of the flow cells." The combined disclosures of Hutchins et al. and Roinestad et al. fail to

teach, suggest, or provide motivation for an apparatus as recited in claim 33, at least for reasons discussed hereinabove with regard to claim 1.

Claims 34 – 38 depend or ultimately depend from claim 33, and recite features not taught, suggested or motivated by the combined disclosures of Hutchins et al. and Roinestad et al., at least for the same reasons as regards claim 33. Claim 37 is further distinguishable for the reasons discussed hereinabove regarding claims 22 – 29.

Claim 39:

Independent claim 39 is directed to a "dissolution media preparation and/or testing apparatus." Claim 39 is distinguishable over Hutchins et al. in view of Roinestad et al. at least for the reasons discussed hereinabove with regard to claim 1.

Claim 40:

Independent claim 40 is directed to a "dissolution system." Claim 40 is distinguishable over Hutchins et al. in view of Roinestad et al. at least for the reasons discussed hereinabove with regard to claim 1.

Conclusion as to rejection of claims 1 – 40 under 35 U.S.C. § 103:

In view of the foregoing, Applicants respectfully submit that claims 1 – 40 are patentable under 35 U.S.C. § 103(a) over Hutchins et al. in view of Roinestad et al., and therefore request that the rejections to these claims be withdrawn at this time.

OTHER CLAIM AMENDMENTS

Apart from the amendments discussed hereinabove, the following is a summary of other claim amendments. These other amendments are believed to be supported by the application as originally filed. Accordingly, no new matter is believed to have been added.

Claim 7 has been amended for the sole purpose of clarifying the course of the recited "optical path", and not in response to a substantive rejection or for any purpose relating to patentability.

Claim 16 has been amended for the sole purpose of clarifying the association among the probes and the optical lines, and not in response to a substantive rejection or for any purpose relating to patentability.

Claim 35 has been amended for the sole purpose of deleting redundant recitation of the "manifold body", and not in response to a substantive rejection or for any purpose relating to patentability.

Docket No.: 01-22 US

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

Respectfully submitted,

THE ECLIPSE GROUP

Date: 1/29/04 By: David P. Gloekler

David P. Gloekler
Registration No. 41,037
Attorney for Applicant
Phone: (919) 419-9922
Fax: (312) 264-5424

CORRESPONDENCE ADDRESS:

Ms. Bella Fishman
Legal Department
Varian, Inc.
3120 Hansen Way, M/S D-102
Post Office Box 10120
Palo Alto, CA 94304-1030

01-12 US
Customer No. **23693**